File No. 6013-149US MHR/kb

Montréal, CANADA,
March 27, 2007

UNITED STATES PATENT AND TRADEMARK OFFICE

Application No	:	10/517,319	
Filing Date	:	July 15, 2005	
Applicant	:	Philippe A. Tessier	
Title of Invention	:	CHEMOTACTIC FACTOR INHIBITOR FOR MODULATING INFLAMMATORY REACTIONS	
Art Unit	:	1656	
Examiner	:	Marsha M. Tsay	Tel: (571) 272-2938
Patent Agent	:	Marie-Hélène Rochon	Tel: (514) 847-6095

Commissioner of Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450
U.S.A.

DECLARATION I

I, **Philippe A. Tessier**, do hereby solemnly declare that:

(1) I am a citizen of Canada and am employed as an associate professor by Laval University in Québec, Canada. A copy of my curriculum vitae is enclosed in Exhibit A.

(2) I am one of the co-inventor of United States patent application serial number 10/517,319 filed on July 15, 2005.

(3) I have read and understood the content U.S. application serial number 10/517,319 as well as the Office Action of October 31, 2006 and the Advisory Action of January 12, 2007.

(4) I have supervised experiments showing that S100A8/A9 heterodimers and S100A9 homodimers have been demonstrated to increase the adhesion of neutrophils to endothelial cells. These experiments are summarized in Exhibit B.

(5) I, the undersigned, declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C §1001 of the United States Code and that such willful false statements may jeopardize the validity of any patent issued for the above-referenced patent application.

Philippe A. Tessier

By: _____ Date: 27 March 2007

EXHIBIT A

CURRICULUM VITAE

PERSONNAL INFORMATION

Name: Tessier, Philippe Alex

Nationality: Canadian

Languages: French, English

EDUCATION

1996-1999: Post-Doctoral Studies, Leukocyte Adhesion Laboratory, Imperial Cancer Research Fund, London, United Kingdom.
Supervisor: Dr Nancy Hogg

1992-1996: Ph.D., Department of Microbiology-Immunology, Faculty of Medicine, Université Laval, Ste-Foy, Québec, Canada.
Supervisor: Dr Paul H. Naccache, Co-Supervisor: Dr Shaun R. McColl

1995: « Visiting Fellow », Department of Microbiology and Immunology, The University of Adelaide, Adelaide, Australia.

1994-1995: « School Visitor », Division of Clinical Sciences, The John Curtin School of Medical Research, The Australian National University, Canberra, Australia.

1990-1992: M.Sc., Department of Physiology-Endocrinology, Faculty of Medicine, Université Laval, Ste-Foy, Québec, Canada.
Supervisor: Dr Shaun R. McColl, Co-Supervisor: Dr Marie Audette.

1987-1990: B.Sc., Department of Biochemistry, Faculty of Sciences, Université Laval, Ste-Foy, Québec, Canada.

ACADEMIC POSITION

1999-2004 Assistant Professor, Department of Medical Biology, Faculty of Medicine, Université Laval

2004-present Associate Professor, Department of Medical Biology, Faculty of Medicine, Université Laval

OTHER ACTIVITY

1997-1998 Scientific writer, Le Matinternet (http://matin.qc.ca/indexcyra.html).

AWARDS

Scholarship

2003-2007 Chercheur-boursier Junior 2, Fonds de la Recherche en Santé du Québec, Canada

1999-2003 Research Scholar, Arthritis Society of Canada, Canada

Post-Doctoral studies

1997-2000 Fellowship, Medical Research Council of Canada, Canada

1997-2000 Fellowship, Imperial Cancer Research Fund, United Kingdom

1997-1999 Fellowship, Arthritis Society of Canada, Canada (declined)

1996-1998 Fellowship Arthritis Society of Canada / Medical Research Council of Canada, Canada (declined)

Ph.D.

1991-1994 Studentship, Fonds de la Recherche en Sante du Québec, Canada

1991-1996 Studentship, Arthritis Society of Canada, Canada

GRANTS

2007-2008 **Effects of S100A8 and S100A9 inhibitors on collagen-induced arthritis**, $50 000, Canadian arthritis network, Canada.
Aim of the study: This grant is aimed at determineing the role of S100A8 and S100A9 in a mouse model of arthritis.

2005-2010 **The Multi-Cellular Basis of Urate-induced Arthropathies**, US$222 000/year, National Institutes of Health, U.S.A., co-investigator.
Aim of the study: This grant is aimed at studying the effect of monosodium urate crystals on leukocytes.

2004-2005 **Blockade of S100A8, S100A9, and S100A12 as a new treatment for arthritis**, $60,000/year, Institute of Musculoskeletal health and arthritis (Canadian Institutes of Health Research), Principal Investigator
Aim of the study: This grant is aimed at generating blockers of S100A8, S100A9, and S100A12 and at testing these inhibitors as new therapeutic avenues for the treatment of arthritis

2003-2006 **Development of a plant based vaccination platform for hepatitis C virus**, $185 404/year, Natural Sciences and Engineering Research Council, Canada, co-investigator.
Aim of the study: This grant is aimed at generating an hepatitis C virus vaccine by modifying the Papaya Mosaic Virus to express hepatitis C virus proteins.

2002-2005 **Role of S100A8, S100A9, and S100A12 in neutrophil migration to inflammatory sites**, Principal Investigator, $98,208/year, Canadian Institutes of Health Reseach, Canada
Aim of this grant: This grant is aimed at cloning, sequencing and

characterising the receptors for S100A8, S100A9, and S100A12.

2000-2001 **Laboratoire d'étude de la migration des leucocytes**. Co-investigator, $195,953 (Total budget $490,294), Canadian Foundation for Innovation, Canada
Equipment grant for the purchase of an intravital videomicroscope and a confocal microscope.

2000-2001 **Starting Fund**, Principal Investigator, $40,000, Régie Régional de la Santé et des Services Sociaux, Canada
Equipment grant

1999-2002 **Inflammation in gout : Role of the MRP proteins**, Principal Investigator, $65,000/year Arthritis Society of Canada, Canada
Aim of the study: This grant was aimed at investigating the involvement of S100A8 and S100A9 in the generation of the inflammatory response associated with gout.

1999-2001 **Rôle des protéines MRP dans l'inflammation de la goutte**. Principal Investigator, $20,000/year, Fonds de la Recherche en Santé du Québec, Canada
Equipment grant

1999-2000 **Persistant Organic Polluants (POPs) et inflammation**. Co-investigator, $15,000 for one year, Réseau de recherche en santé environnementale – FRSQ, Canada
Aim of the study : This grant was a pilot study of the effect of the POPs dieldrin and toxaphen on human neutrophil functions.

1999 **Subvention de démarrage**, Principal Investigator, $15,000, Centre de Recherche du CHUL
Equipment grant

RESEARCH CONTRACTS

2001-2003 Use of MRPs to induce neutrophilia. Principal Investigator, $238,600, Innovatech-Québec, Canada

PUBLICATIONS

1. K. Mitchell1, H.-Y.T. Yang, P.A. Tessier, W. Taylor Muhly, W.D. Swaim, I. Szalayova, J.M. Keller, E. Mezey, M.J. Iadarola. S100A8- and S100A9-secreting leukocytes in spinal cord during peripheral tissue inflammation: implications to pain. *Nature Neurol.*, **submitted.**
2. E. Lorenz, M. Muehlebach, **P.A. Tessier**, N. Alexis, R.D. Hite, M.C. Seeds, D.B. Peden, W. Meredith. Expression of S100A8/A9 and S100A12 in acute and chronic lung diseases. *Am. J. Resp. Crit. Care Med.*, **submitted**.

3. M.-A. Raquil, N. Anceriz, P. Rouleau, **P.A. Tessier**. Blockade of antimicrobial proteins S100A8 AND S100A9 inhibits phagocytes migration to the alveoli in streptococcal pneumonia. *J. Immunol.*, **conditionally accepted**.
4. F. Kukulski, F. Ben Yebdri, J. Lefebvre, M. Warny, **P.A. Tessier**, J. Sévigny. 2007. Extracellular nucleotides mediate LPS-induced neutrophil migration in vitro and in vivo. *J. Leuk. Biol.*, **in press.**
5. J. Denis, N. Majeau, E. Acosta-Ramirez, C. Savard, M.-C. Bedard, S. Simard, K. Lecours. M. Bolduc, C. Paré, B. Willems, N. Shoukry. **P.A. Tessier**, P. Lacasse, A. Lamarra, R. Lapointe, C. Lopez Macias. D. Leclerc. 2007. Immunogenicity of papaya mosaic virus like particles fused to a hepatitis c virus epitope: evidence for the critical function of multimerization. *Virology*, **in press.**
6. N. Anceriz, K. Vandal, **P.A. Tessier.** 2007. S100A9 mediates neutrophil adhesion to fibronectin through activation of beta2 integrins. *Biochem Biophys Res Commun.* **354**(1):84-9.
7. J.N. Jarvis, H.R. Petty, Y. Tang, M.B. Frank, **P.A. Tessier**, I. Dozmorov, K. Jiang, A. Kindzelski, Y. Chen, C. Cadwell, M. Turner, P. Szodoray, J.L. McGhee, M. Centola. 2006. Evidence for chronic, peripheral activation of neutrophils in polyarticular juvenile rheumatoid arthritis. *Arthritis Res. Ther.* **8**(5):R154.
8. K. Greenlee, D.B. Corry, D. Engler, R. Matsunami, **P.A. Tessier**, R.G. Cook, Z. Werb|, F. Kheradmand. 2006. Identification of In Vivo Substrates For MMP2/MMP9 Reveals A Mechanism For Resolution of Inflammation. *J. Immunol.* **177**(10):7312-21.
9. A. Hermani, B. De Servi, S. Medunjanin, **P.A. Tessier**, D. Mayer. 2006. S100A8 and S100A9 activate MAP kinase and NF-kappaB signaling pathways and trigger translocation of RAGE in human prostate cancer cells. *Exp. Cell Res.* **312**(2):184-97.
10. S. Bozinovski, M. Cross, R. Vlahos, J.E. Jones, K. Hsuu, **P.A. Tessier**, D.A. Hume, J.A Hamilton, C.G. Geczy, G.P. Anderson. 2005. Proteomic analysis identifies S100A8 as a glucocorticopid resistant determinant of neutrophilic lung inflammation in vivo. ***J. Proteomic Res.*** **14**(4): 136-145.
11. E. Lorenz, D.C. Chemotti, K. Vandal, **P.A. Tessier**. 2004. Toll-like receptor 2 represses nonpilus adhesin-induced signaling in acute infections with the *Pseudomonas aeruginosa pilA* mutant. ***Infect. Immun.*** **72**(8): 4561-4569.
12. C. Ryckman, C. Gilbert, R. de Médicis, A. Lussier, K. Vandal, **P.A. Tessier**. 2004. Monosodium urate monohydrate crystals induce the release of the proinflammatory protein S100A8/A9 from neutrophils. ***J. Leukoc. Biol.***, **76**(2): 433-440.
13. M. Jaramillo, I. Plante, N. Ouellet, K. Vandal, **P.A. Tessier**, M. Olivier. 2004. Hemozoin-inducible proinflammatory events in vivo: potential role in malaria infection. ***J. Immunol.***, **172**(5) :3101-3110.
14. K. Vandal, P. Rouleau, A. Boivin, C. Ryckman, M. Talbot, **P.A. Tessier**. 2003. Blockade of S100A8 and S100A9 suppresses neutrophil migration in response to LPS. ***J. Immunol.*** **171**(5):2602-2609.

15. C. Ryckman, S.R. McColl, K. Vandal, R. de Médicis, A. Lussier, P.E. Poubelle, **P.A. Tessier**. 2003. Role of S100A8 and S100A9 in neutrophil recruitment in response to monosodium urate crystals in the air pouch model of acute gouty arthritis. ***Arthritis Rheum.*, 48**(8): 2310-2320.
16. P. Rouleau, K. Vandal, C. Ryckman, P.E. Poubelle, A. Boivin, M. Talbot, **P.A. Tessier**. 2003. The calcium-binding protein S100A12 induces neutrophil adhesion, migration, and release from bone marrow in mouse at concentrations similar to those found in human inflammatory arthritis. ***Clin. Immunol.* 107**(1): 46-54.
17. C. Ryckman, K. Vandal, P. Rouleau, M. Talbot, **P.A. Tessier.** 2003. Proinflammatory activities of S100 proteins: S100A8, S100A9 and S100A8/A9 stimulate neutrophil chemotaxis and adhesion. ***J. Immunol.* 170**(6):3233-3242.
18. C. Ryckman, G.A. Robichaud, J. Roy, R. Cantin, M.J. Tremblay, **P. A. Tessier**. 2002. HIV-1 transcription and virus production are both accentuated by the proinflammatory myeloid related proteins in human CD4+ T lymphocytes. ***J. Immunol.* 169**(6): 3307-3313.
19. M. Robinson, P.A. Tessier, R. Poulson, N. Hogg. 2002. The S100 family heterodimer, MRP-8/14, binds with high affinity to heparin and heparan sulphate glycosaminoglycans on endothelial cells ***J. Biol. Chem.*, 277**(5): 3658-3665
20. M. Pelletier, C. J. Roberge, M. Gauthier, K. Vandal, **P.A. Tessier**, D. Girard. 2001. Activation of human neutrophils *in vitro* and dieldrin-induced neutrophilic inflammation *in vivo*. ***J. Leuk. Biol.*, 70**(3): 367-373.
21. R. Henderson, L.H.K. Lim, **P.A. Tessier**, M. Mathies, M. Perretti and N. Hogg. 2001.The use of LFA-1 deficient mice to determine the role of LFA-1, Mac-1 and α4 integrin in the inflammatory response of neutrophils. ***J. Exp. Med.*, 194**(2): 219-226
22. M. Gauthier, C.J. Roberge, M. Pelletier, **P.A. Tessier**, D. Girard. 2001. Activation of human neutrophils by technical toxaphene. ***Clin. Immunol. Immunopathol.*, 98**(1):46-53.
23. **P.A. Tessier**, P.H. Naccache, K.R. Diener, R.P. Gladue, K.Neote, I. Clarke-Lewis, S.R. McColl. 1998. Induction of acute inflammation in vivo by Staphylococcal superantigens. II. Critical role for chemokines, ICAM-1, and TNFα. ***J. Immunol.*, 161**(3): 1204-1211.
24. K.D. Diener, **P.A. Tessier**, J.D. Fraser, F. Kontgen, S.R. McColl. 1998. Induction of acute inflammation in vivo by staphylococcal superantigens I. Leukocyte recruitment occurs independently of T lymphocytes and major histocompatibility complex Class II molecules. ***Lab. Invest.*, 78**(6): 647-656.
25. **P.A. Tessier**, K.R. Diener, P.H. Naccache, R.P. Gladue, K. Neote, I. Clarke-Lewis, S.R. McColl. 1997. Chemokine networks *in vivo*: Involvement of both C-X-C and C-C chemokines in neutrophil extravasation in response to tumour necrosis factor α. ***J. Immunol.* 159**(7): 3595-3602.
26. **P.A. Tessier**, P. Cattaruzzi, S.R. McColl. 1996. Inhibition of lymphocyte adhesion to cytokine-activated synovial fibroblasts by glucocorticoids involves the attenuation of vascular cell adhesion molecule 1 and intercellular

adhesion molecule 1 gene expression. ***Arthritis Rheum.*** **39**(2): 226-234.

27. **P.A. Tessier**, M. Audette, P. Cattaruzzi, S.R. McColl. 1993. Upregulation by tumor necrosis factorα of intercellular adhesion molecule-1 expression and function in synovial fibroblasts and its inhibition by glucocorticoids. ***Arthritis Rheum.*** **36**(11):1528-39.
28. M. Bouillon, **P. Tessier**, R. Bouliane, R. Destrempe, M. Audette. 1991. Regulation by retinoic acid of ICAM-1 expression on human tumor cell lines. ***Biochem Biophys Acta*** **1097**(2): 95-102.

BOOK CHAPTERS

1. P.A. Tessier, D. Girard. 207. in *Inflammation and neutrophils: A short introduction.* D. Girard Ed. Research Signpost, Kerala, India.
2. N. Anceriz, M.A. Raquil, **P.A. Tessier**. 2007. The proinflamamtory functions of S100A8, S100A9, and S100A12. in *Phenotypic and functional changes of neutrophils activated by recently identified modulators.* D. Girard Ed. Research Signpost, Kerala. India.

SEMINARS

1. Extracellular activities of S100A8, S100A9, and S100A12. NovoNordisk, Copenhagen, Denmark. 9 February 2004
2. Les protéines S100: de petites protéines aux grands destins. Centre de Recherche du CHUL, Quebec city, Canada. 5 February 2004
3. Les myeloid related proteins et la goutte. INRS/IAF-Santé humaine, Montreal, Canada. 15 February 2000.
4. Les MRPs : nouveaux acteurs dans la migration leucocytaires. Centre de Recherche du CHUL, Quebec city, Canada. 2 April 1998
5. Les MRPs et la réaction inflammatoire. INRS-Santé, Montreal, Canada. 12 March 1998
6. Chemokine gene expression in a murine model of leukocyte recruitment to extravascular sites. Medicity, University of Turku, Finland. 12 July 1996.
7. Chemokine gene expression in a murine model of leukocyte recruitment to extravascular sites. The Imperial Cancer Research Fund, London, U.K. 10 July 1996.
8. Chemokine gene expression in a murine model of leukocyte recruitment to extravascular sites. William Harvey Research Institute, London, U.K. 9 July 1996.

ABSTRACTS

1. M.-A. Raquil, N. Anceriz, **P.A. Tessier**. Les protéines S100 et la migration des leucocytes au site infectieux. 48th Congrès du Club de Recherche Clinique du Québec, Lac-à-l'Eau-Claire, Canada, September 2006.
2. M.-A. Raquil, K. Vandal, P. Rouleau, **P.A. Tessier**. S100A8, S100A9, and S100A12 stimulate the proliferation of hematopoietic cells. 12th International

Congress of Immunology and 4th Annual Conference of FOCIS, Montreal, Canada, July 2004.

3. N. Anceriz, K. Vandal, **P.A. Tessier**. Different effects of S100A8, S100A9, and S100A12 on neutrophil adhesion to endothelial cells and extracellular matrix proteins. 12th International Congress of Immunology and 4th Annual Conference of FOCIS, Montreal, Canada, July 2004.
4. J. Denis, P. Rouleau. K. Vandal, **P.A. Tessier,** D. Leclerc. The plant potexvirus Papaya Mosaic Virus triggers a strong immune response in mouse. 12th International Congress of Immunology and 4th Annual Conference of FOCIS, Montreal, Canada, July 2004.
5. K. Vandal, C. Ryckman, P. Rouleau, **P.A. Tessier**. The chemotactic factors S100A8 and S100A9 are involved in neutrophil release from bone marrow and migration to the inflammatory site in response to LPS. 17th Annual Spring Meeting of the Canadian Society for Immunology, Lake Louise, Canada, March 2003.
6. C. Ryckman, R. Cantin, G. Robichaud, M.J. Tremblay, **P.A. Tessier**. The pro-inflammatory Myeloid Related Proteins activate HIV replication in infected T-lymphocytes. 9th Conference on retroviruses and opportunistic infections. Seattle, USA, February 2002.
7. C. Ryckman, K.Vandal, P.Rouleau, M.Talbot, **P.A.Tessier**. Myeloid related proteins are associated with neutrophil accumulation induced by monosodium urate crystals. Stockholm, Sweden, July 2001.
8. C.J. Roberge, M. Gauthier, V. Lavaste, **P.A. Tessier,** D. Girard. Activation of human neutrophils *in vitro* and induction of neutrophilic inflammation *in vivo* by toxaphene. Canadian Society of Immunology 15th Annual Meeting, Lake Louise, Canada, April 2001.
9. M. Gauthier, C.J. Roberge, **P.A. Tessier**, D. Girard. Propriétés pro-inflammatoires du toxaphène *in vivo* et *in vitro*. Colloque annuel du Centre de recherche en toxicologie de l'environnement (TOXEN), Montréal, Canada, December 2000.
10. M. Pelletier, **P.A. Tessier,** D. Girard. Activation des neutrophiles *in vitro* et induction d'une inflammation neutrophillique *in vivo* par le dieldrine. Colloque annuel du Centre de recherche en toxicologie de l'environnement (TOXEN), Montréal, Canada December 2000.
11. **P.A. Tessier**. Les Myeloid Related Proteins et la réponse inflammatoire, 68e congrès de l'Association Canadienne-Française pour l'Avancement des Sciences, Montréal, Canada, May 2000
12. C. Ryckman, K. Vandal, **P.A. Tessier**. Sécrétion des protéines MRP (Myeloid Related Proteins) par les neutrophiles activés avec les crystaux d'urate monosodique (MSU). 68e congrès de l'Association Canadienne-Française pour l'Avancement des Sciences, Montréal, Canada, May 2000
13. C. Ryckman, K. Vandal **P.A. Tessier**. Secretion of myeloid related proteins (MRP) by monosodium urate crystal-stimulated neutrophils. Canadian Society of Immunology. Bromont, Canada, March 2000.
14. R.D. May, **P.A. Tessier**, M J. Robinson, N. Hogg. A functional investigation of the murine S100 protein MRP-14, *in vitro* and *in vivo*. Inflammation Paris

99, Paris, France, June 1999.

15. R.D.May, **P.A. Tessier**, M.J. Robinson, N. Hogg. A functional investigation of the murine S100 protein MRP-14, *in vitro* and *in vivo*. Workshop on neutrophil development and functions. Madrid, Spain, April 1999.
16. R. May, **P.A. Tessier**, M. J. Robinson, N. Hogg. Expression of murine MRP-14: *in vitro* and *in vivo* functions. Imperial Cancer Research Fund Annual Colloquium, Warwick, U.K., April 1998.
17. N. Hogg, A. McDowall, **P.A. Tessier**, R. Newton. Regulation of β_2 integrin function. Keystone meeting on leukocyte-endothelium adhesion. Lake Tahoe, Colorado, U.S.A., March 1998.
18. **P.A. Tessier**, P.A Hessian, R. Poulson, N. Hogg. Myeloid cells releases MRP proteins onto endothelium. 12th Spring meeting of the Canadian Society for Immunology, Sainte-Adèle, Canada, March 1998.
19. **P.A. Tessier**[1], P.H. Naccache, K. Neote, S.R. McColl. Induction by TNFα of chemokine gene expression in a murine model of leukocyte recruitment to extravascular sites. 10th Spring meeting of the Canadian Society for Immunology, Sainte-Adèle, Canada, March 1996.
20. **P.A. Tessier**, P.H. Naccache, K. Neote, S.R. McColl. Chemokine gene expression in a murine model of leukocyte recruitment to extravascular sites. Chemotactic cytokines: Targets for novel therapeutic development, Philadelphia, Pennsylvania, U.S.A., October 1995.
21. **P. Tessier**, S.R. McColl. Involvement of both ICAM-1 and VCAM-1 in the adhesion of monocytes and lymphocytes to synovial fibroblasts. Joint Meeting of the American Association of Immunologists and the Clinical Immunology Society, Denver, Colorado, U.S.A.., May 1993.
22. **P. Tessier**[1], M. Audette, S.R. McColl. Regulation by tumor necrosis factor a of intercellular adhesion molecule-1 gene expression in human synovial fibroblasts. Annual Meeting of the Royal College of Physicians and Surgeons of Canada, Quebec city, Canada, September 1991.
23. **P. Tessier**, M. Audette, S.R. McColl. Regulation by tumor necrosis factor α of intercellular adhesion molecule-1 gene expression in human synoviocytes. Federation of American Societies for Experimental Biology, Atlanta, U.S.A.., April 1991.
24. M. Audette, M. Bouillon, **P. Tessier**. Stimulated expression of intercellular adhesion molecule-1 (ICAM-1) by retinoic acid on human tumor cell lines. Karger Symposium "Cell to Cell Interaction", Basel, Switzerland, August 1990.
25. M. Bouillon, N. Liao, **P.Tessier**, M. Audette. Expression de la ICAM-1 sur des lignées de tératocarcinomes humains et régulation de son expression par l'acide rétinoïque. Association Canadienne-Française pour l'Avancement des Sciences, 58ième Congrès, Quebe cityc, Canada, May 1990.

OTHER ACTIVITIES

[1]Selected for oral presentation in a workshop.

2005-2006 Member, STIHR Mid-Term Review Committee, CIHR
2003 Organiser, Microbiology, Virology and Immunology section, 71st ACFAS meeting, Rimouski, May 2003
2002-2004 Organiser, Social activities, 12 International Congress of Immunology, Montreal, July 2004
2002 Organiser, Microbiology, Virology and Immunology section, 70th ACFAS meeting, Quebec city, May 2002
2001-2002 Member, Immunology Committee, Arthritis Society grant program
2000 Invitee, Immunology Committee, Arthritis Society grant program

STUDENTS

1. Jérôme Denis, Ph.D. (co-supervisor), Microbiology-Immunology, Faculty of Medicine, Université Laval, 2003-present.
2. Marie-Astrid Raquil, Ph.D., Microbiology-Immunology, Faculty of Medicine, Université Laval, 2003-present.
3. Nadia Anceriz, Ph.D., Microbiology-Immunology, Faculty of Medicine, Université Laval, 2003-present.
4. Carle Ryckman, Ph.D., Microbiology-Immunology, Faculty of Medicine, Université Laval, 1999-present.
5. Pascal Rouleau, M.Sc., Microbiology-Immunology, Faculty of Medicine, Université Laval, 2002-2003.

THESIS (REFEREE)

Ph.D.

1. Carle Ryckman
   Microbiology-Immunology, Faculty of medicine, Université Laval, 25 February 2004

   Supervisor

2. Claudine Matte
   Microbiology-Immunology, Faculty of medicine, Université Laval, 15 February 2000
   Examinator

Master's.

1. Alain Boulende, Microbiology-Immunology, Faculty of medicine, Université Laval, 20 October 2006, Co-supervisor
2. Jean-François Gauthier, Microbiology-Immunology, Faculty of medicine, Université Laval, 4 October 2006, Examinator
3. Caroline Bélanger, Pharmacie, Faculté de pharmacie, Université de Montréal, 22 August 2006, Examinator
4. Valérie Garceau, Microbiology-Immunology, Faculty of medicine,

Université Laval, 15 September 2003, Examinator
5. Claude Ratthé, INRS-IAF/Santé humaine, 3 June 2003, Examinator
6. Andrée Maheux, Microbiology-Immunology, Faculty of medicine, Université Laval, 10 February 2003, Examinator
7. Pascal Rouleau, Microbiology-Immunology, Faculty of medicine, Université Laval, 22 Janary 2003, Supervisor
8. Julie Nieminen, Microbiology-Immunology, Faculty of medicine, Université Laval, 17 January 2003, Examinator
9. Geneviève Lachance, Microbiology-Immunology, Faculty of medicine, Université Laval, 24 April 2002, Examinator
10. Marc Gauthier, INRS-IAF/Santé humaine, 15 October 2001, Examinator
11. Valérie Lavastre, INRS-IAF/Santé humaine, 17 September 2001, Examinator
12. Frédéric Dallaire, Microbiology-Immunology, Faculty of medicine, Université Laval, 14 February 2001, Examinator
13. Martin Pelletier, INRS-IAF/Santé humaine, 29 September 2000, Examinator
14. Philippe Desaulniers, Microbiology-Immunology, Faculty of medicine, Université Laval, 19 June 2000, Examinator
15. Isabelle Filion, Microbiology-Immunology, Faculty of medicine, Université Laval, 20 October 1999,Examinator

COURSES

2003-present Collaborator to the graduate course: La reaction inflammatoire
2000-present Collaborator to the graduate course: Immunopathogénèse des maladies infectieuses
2000-présent Collaborator to the graduate course: Immunologie cellulaire

EXHIBIT B

Endothelial cells (ECV) were cultured in 96-well plates in M199-10% Foetal Bovine Serum until confluent. After washing, 25 µl of M199 were added to the wells and then 25 µl of S100 proteins (10 µg/ml) or fMLP 10^{-6} M as a positive control. Neutrophils were resuspended at 5 X 10^6 cells/ml in M199 and labelled with 5 µM intracellular fluorescent dye calcein-AM for 30 min at 37°C. After washing, 10 µl of the cell suspension were added to the wells, allowed to adhere for 30 min at 37°C before being washed three times by immersion in cold PBS. The adherent cells were lysed by adding dH_2O, and fluorescence was measured at λex = 485 nm and λem = 530 nm using a 96-well plate fluorescence reader. In some experiments, neutrophils or endothelial cells were pre-incubated for 30 min with 10 µg/ml of S100 proteins, washed and the adhesion assay was performed as described.

As shown in figure 1, S100A9 and S100A12 stimulate neutrophil adhesion to endothelial cells. However, S100A8 does not induce neutrophil adhesion. In addition, S100A8/A9 induces neutrophil adhesion to endothelial cells at a level similar to S100A9.

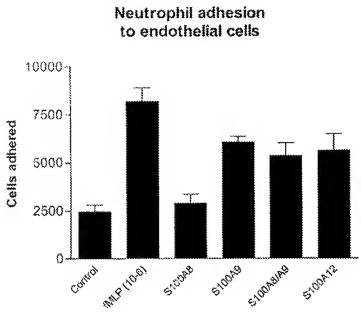

Figure 1: Effect of S100A8, S100A9 and S100A12 on neutrophils adhesion to endothelial cells. Neutrophils adhesion was measured in 96-well plates with confluent endothelial cells in presence of increasing concentrations of S100A8, S100A9, S100A12 or fMLP 10^{-6} M as positive control. The cells were lysed in dH_2O and the percentage of adherent cells was assessed. Data represent the mean ± SEM of at least 3 experiments performed on different blood donors.

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Montréal, CANADA,
March 27, 2007

UNITED STATES PATENT AND TRADEMARK OFFICE

Application No	:	10/517,319	
Filing Date	:	July 15, 2005	
Applicant	:	Philippe A. Tessier	
Title of Invention	:	CHEMOTACTIC FACTOR INHIBITOR FOR MODULATING INFLAMMATORY REACTIONS	
Art Unit	:	1656	
Examiner	:	Marsha M. Tsay	Tel: (571) 272-2938
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Commissioner of Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450
U.S.A.

DECLARATION II

I, **Philippe A. Tessier**, do hereby solemnly declare that:

(1) I am a citizen of Canada and am employed as an associate professor by Laval University in Québec, Canada. A copy of my curriculum vitae is enclosed in Exhibit A of declaration I, enclosed herewith.

(2) I am one of the co-inventor of United States patent application serial number 10/517,319 filed on July 15, 2005.

(3) I have read and understood the content U.S. application serial number 10/517,319 as well as the Office Action of October 31, 2006 and the Advisory Action of January 12, 2007.

(4) Exhibit C is a report that was generated in response to my application for funds from the Fonds de la Recherche en Santé du Québec (F.R.S.Q.). This exhibit

shows that it was not obvious that these proteins played roles in inflammatory reactions.

(5) High serum concentrations of S100 proteins have been shown to occur in pathologies associated with increased numbers and/or activities of neutrophils. Elevated levels of S100A8/A9 (more than 1 μg/mL) are observed in the serum of patients suffering from various infections and inflammatory pathologies such as cystic fibrosis, tuberculosis, Crohn disease, and juvenile rheumatoid arthritis. They are also expressed at very high levels in the synovial fluid and plasma of patients with from rheumatoid arthritis and gout. All these data indicate an association between S100A8, S100A9, and S100A12 and inflammatory pathologies, but it was not clear if their presence was a mere reflection of inflammation or if they participated actively in the development of the inflammatory response. In fact, experts in the fields of inflammation and S100 proteins were sceptical of their role in inflammation.

(6) For example, Dr Nancy Hogg from the Cancer Research UK has been studying S100A8, S100A9, and S100A12 for more than 20 years. She was one of the first to describe the presence of these proteins in inflammation and has recently reported that S100A9 stimulates neutrophil adhesion to fibrinogen. However, she remains convinced that the extracellular presence of S100A8, S100A9, and S100A12 is a consequence of inflammation, rather than a cause of inflammation. Indeed, she was convinced that S100 proteins are released by cell necrosis, rather than by active secretion (see Exhibit C – page 7, 3rd paragraph). This scepticism is also exemplified in the evaluation report of a research proposal by a reviewer who says that "If MRP secretion initiates gout, it is important to establish exactly what effects MRPs have on neutrophil activity" (see Exhibit C – page 10, 3rd paragraph).

(7) For a long time, the proinflammatory activities of the MRPs remained elusive. One explanation for this is the fact that the scientific literature was very confusing. For example, Newton and Hogg (enclosed in the I.D.S submitted concurrently) demonstrated that human S100A9 stimulates neutrophil adhesion to fibrinogen by activating the β2 integrin Mac-1 (CD11b/CD18). The promotion of

this adhesion was negatively regulated by the formation of the heterocomplex with S100A8 implying that S100A8 as well as S100A8/A9 do not stimulate neutrophil adhesion. Eue et al. (submitted in the I.D.S. submitted concurrently) also reported that S100A8 do not enhanced monocyte adhesion to endothelial cells. However, contrarily to the latter study they demonstrated that not only S100A9, but also S100A8/A9 enhanced monocyte adhesion to endothelial cells via Mac-1/ICAM-1 interactions. Thus, these results directly contradicted Newton and Hogg's report by suggesting that S100A8 does not negatively regulate S100A9 activity by forming S100A8/A9.

(8) Studies carried out using murine MRPs demonstrated that CP-10 is a potent chemotactic factor for neutrophils, and induces sustained leukocyte recruitment in vivo. Moreover, like human S100A9, CP-10 does not stimulate calcium flux, shedding of L-selectin, or upregulation of the β2 integrin Mac-1 on neutrophils. However, contrarily to its putative murine homologue, human S100A8 is supposedly not chemotactic for neutrophils, but has been reported to be chemotactic for periodontal ligament cells.

(9) Therefore, even today, the exact activities of S100A8 and S100A8/A9 remain unknown, particularly their effects on neutrophil migration. Harrison et al. (submitted in the I.D.S. submitted concurrently) showed that CP-10 chemotactic activity can be efficiently inhibited by oxidation of the protein, demonstrating a certain susceptibility of CP-10 to inactivation. S100A9 activity appeared to be differently affected by oxidation. The discrepancies in MRP activity could therefore be due to differences in protein activity arising from interlaboratory variation in purification protocols or methodologies.

(10) The discrepancies in S100 protein activities described by others might be due to oxidation and consequently deactivation of the protein during purification. The presence of denaturing agents such as DTT or imidazole during the purification process could result in their inactivation. We hypothesized that the discrepancies in MRPs activities could have resulted from interlaboratory variance in methodology; in particular, protein oxidation or denaturation during the purification process or during their manipulation, that could be responsible for

the inactivation of the MRPs. With the collaboration of my research team, I thus devised new protocols for the purification of S100A8, S100A9, and S100A12 which did not necessitate the use of denaturating agents. I began working on these new protocols in July 1999, and obtained the first recombinant proteins a year later, in spring 2000. I next generated blocking antibodies for murine and human S100A8, S100A9, and S100A12. These reagents enabled us to determine that S100A8, S100A9, and S100A12 exert proinflammatory functions once released in the extracellular environment. The demonstration of the efficacy of anti-S100A8 and anti-S100A9 antibodies to block inflammatory reactions was completed in the spring 2001.

(11) In a nutshell, it took me at least (2) years of work to demonstrate the role of S100A8 and S100A9 in inflammation.

(12) I, the undersigned, declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C §1001 of the United States Code and that such willful false statements may jeopardize the validity of any patent issued for the above-referenced patent application.

Philippe A. Tessier

By: _____ Date: 27 March 2004

RAPPORT D'ÉVALUATION EXTERNE
BOURSE DE CHERCHEUR-BOURSIER et CHERCHEUR CLINICIEN
FONDS DE LA RECHERCHE EN SANTÉ DU QUÉBEC

RAPPORT DE L'ÉVALUATEUR / REFEREE'S REPORT:

Vous êtes invité(e) à utiliser le système de cotation suivant: / The criteria to be evaluated, kindly use the following rating system:

Exceptionnel / Exceptional	*Moyen / Average*
Excellent / Excellent	*Faible / Weak*
Très bon / Very Good	*Rejet / Reject*
Bon / Good	

1. ÉVALUATION DU PROGRAMME DE RECHERCHE POUR LES QUATRE (4) PROCHAINES ANNÉES - EVALUATION OF THE RESEARCH PROGRAM FOR THE NEXT FOUR (4) YEARS.

VOUS ÊTES INVITÉ(E) À ÉVALUER: - PLEASE EVALUATE:

1.1 Les objectifs des projets de recherche. **(Faire ressortir les points forts et les points faibles)** - The objectives of the research projects . **(Emphasize the strong and weak points)**

1.2 La revue de la littérature . - The review of the literature .

1.3 Le protocole de recherche . - The research protocol .

1.4 La méthodologie de recherche. - The research methodology.

1.5 L'originalité des projets et du programme de recherche. - The originality of the research program.

2. **Selon les critères évalués précédemment, diriez-vous que la présente demande est excellente, très bonne, bonne, faible ou mérite d'être rejetée. / Following the evaluation of this application, according to the above criteria would you rate this application as excellent, very good, good, poor or merits rejection.**

(Commentaires obligatoires si la demande est faible ou rejetée / Additional comments are required if the application is judged to be poor or is rejected.)

La loi 65 sur l'accès aux documents des organismes publics et sur la protection des renseignements personnels permet au (à la) candidat(e) un droit d'accès à un exemplaire non expurgé du présent rapport. Veuillez noter que copie des commentaires sera automatiquement expédiée. Si vous signez ce rapport ou désirez vous identifier de façon quelconque, le (la) candidat(e) en sera automatiquement informé(e).
The Act respecting access to documents held by public bodies and the protection of personal information provides that an applicant has the right to have access to an unexpurgated copy of this report. Please note that a copy will be automatically sent to the applicant. If you sign this report or otherwise identify yourself in this report, the applicant will be automatically informed.

Signature de l'évaluateur (optionnelle)
Signature of referee (facultative)

Fonds de la recherche en santé du Québec
550, rue Sherbrooke est, 19e étage
Montréal (Québec)
H3A 1B9

RAPPORT D'ÉVALUATION EXTERNE

DEMANDE DE BOURSE DE CHERCHEUR-BOURSIER

FRSQ: 4601 (e)

IDENTIFICATION DU (DE LA) CANDIDATE / APPLICANT IDENTIFICATION

Candidat	Dossier	Catégorie	Nombre d'années d'expérience
Tessier, Philippe A	990111	Junior 1	0 an

RAPPORT DE L'ÉVALUATEUR / REFEREE'S REPORT

Utilisez cette feuille comme première page de votre évaluation ou sinon, prenez soin de bien **reproduire** les informations ci-dessus, soit: l'identification du programme, du candidat ainsi que le numéro apparaissant **dans la case "FRSQ"**. Ajoutez des feuilles au besoin. Votre signature est facultative. **Ce rapport doit être dactylographié.**

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Dr. Philippe Tessier received his Ph.D. in 1996 (University of Laval) and subsequently went on to do a post-doctoral fellowship with Dr. Nancy Hogg in the UK. Based on an observation made there he proposes to investigate the impact of monosodium urate crystals (MSU) on the secretion of two proteins of the S100 family, known as MRP-8 and 14.

The strengths of the proposal lie with the novel observation the MSU causes neutrophils to release MRP-8 and MRP-14 in 30 minutes as well as the extremely ambitious research plan to capitalize on this finding. From his publications as a Ph.D. student and from the letters attached he appears to be a hard working individual and has expertise with many of the techniques he proposes to use.

The main weaknesses of the proposal are two fold -

1) the research plan appears to be premature. As pointed out by Dr. Hogg in her letter, the release may be due to direct damage to the neutrophils via the MSU. Since neutrophils rapidly undergo apoptosis ex vivo, he should verify his findings with monocytes which may be less likely to be damaged by external stimuli (or at least less likely to undergo rapid apoptosis), before embarking on this very ambitious research course
2) The research plan should be better focused and better thought out. For example, why would he want to look at the mRNA levels when the MSU is clearly causing a release of the already stored proteins? There does not appear to be a good rational for the FcγR3 studies. What would be the mechanism or pathway whereby MSU would implicate antibodies and thus the FcγR3 pathway in 30 minutes? He also does not provide information about the sources of his human neutrophils and monocytes, nor does he provide information about the strains of mice he proposes to study. He should propose half the experiments with much more care to detail.

Dr. Tessier provides an adequate overview of the literature, however, he fails to mention that there are other possible chemotactic factors released by MSU stimulated neutrophils/monocytes such as C5a and the crystal induced chemotactic factor (see Spilberg J. Clin. Invest. 1977, 59:582). The latter may be the same as MRP-8, but the old literature may help in terms of study design. In addition, more discussion of the differences between neutrophils ex vivo and in vivo, would have strengthened the proposal.

The research proposal is extremely ambitious, and as mentioned would be much better if it were more focused. Virtually every possible aspect of neutrophil biology (other than apoptosis) is covered but with only sketchy details. As well, he plans to not only investigate the impact of MSU but many other agents such as chemokines, LPS, fMLP, LTB4, PAF, GM-CFS, any of which could be the basis of an entire proposal.

The methodologies proposed are fairly straight forward, and Dr. Tessier has the expertise to do most of them. His group that he is joining will be also able to help him, and he makes mention of future collaborations.

This is a highly original proposal, and if verified could generate very interesting an novel data.

Overall the proposal ranks as **Average**. Dr. Tessier would benefit from a mentor or senior scientist reading through his proposal and discussing it with him. In this way the pitfalls of many young ambitious investigators could be avoided (overly ambitious, lack of focus). In addition, this proposal appears to be premature. With a little more preliminary data along with more publications from his post-doctoral years, this proposal would clearly be strengthened.

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Montréal (Québec)
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RAPPORT D'ÉVALUATION EXTERNE

DEMANDE DE BOURSE DE CHERCHEUR-BOURSIER

FRSQ: 4711 (e)

IDENTIFICATION DU (DE LA) CANDIDATE / APPLICANT IDENTIFICATION

Candidat	Dossier	Catégorie	Nombre d'années d'expérience
Tessier, Philippe A.	990111	Junior 1	0 an

RAPPORT DE L'ÉVALUATEUR / REFEREE'S REPORT

Utilisez cette feuille comme première page de votre évaluation ou sinon, prenez soin de bien reproduire les informations ci-dessus, soit: l'identification du programme, du candidat ainsi que le numéro apparaissant **dans la case "FRSQ"**. Ajoutez des feuilles au besoin. Votre signature est facultative. **Ce rapport doit être dactylographié.**

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Tessier, Philippe, dossier: 99011, Catégorie: Junior 1, 0 ans, FRSQ: 4711 (e)

Objectives: Excellent.
Dr. Tessier has been working on proteins called MRPs which are abundant in neutrophils and to a lesser extent in monocytes. They are cytosolic, but can be secreted via a mechanism that involves tubulin. MRP8(murine) is highly chemotactic, and MRP14(human) promotes neutrophil adhesion. MSU (sodium urate) is well known to cause gout by attracting neutrophils into joints,however the mechanism by which MSU does this is unclear and cannot be fully explained through conventional pathways. Dr. Tessier proposes that MSU may promote MRP secretion and the consequent accumulation of activated neutrophils.

Review of the Literature. Very good.

Protocol. Excellent.
This is a multipronged approach. First the secretion of MRPs by neutrophils will be characterized with particular reference to whether phagocytosis is an obligatory step in MRP secretion. CD16 and CD18 have been implicated as necessary for MSU action. Dr. Tessier will assess the monoclonal antibodies against this molecules will impair MSU driven MRP secretion. He will examine the mechanism through which MSU acts on MRP secretion with respect to (a) cytoskeletal activation and (b) signal transduction pathways.
If MRP secretion initiates gout, it is important to establish exactly what effects MRPs have on neutrophil activity. Dr. Tessier will exammine several parameters, including adhesion, migration, superoxide production, degranulation, and protein synthesis. In the final test of the hypothesis sterile air sacs will be made subcutaneously into which Dr. Tessier will instill various agents including MSU, MRP, and MSU plus MRP antibodies. MSU will induce a neutrophil infiltrate; if this has a obligatory requirement for MRP, it should be possible to block, or attenuate the infiltration with the antisera (if successful the potential clinical application of this concept should be considerable).

Methodology. Excellent.

The only minor criticism I have is that Dr. Tessier refers to bibutyrl cAMP and forskolin as cAMP inhibitors, whereas they are agonists, but I suspect this was an inadvertent error. The air sac methodology is very elegant and despite its apparent simplicity should provide a powerful experimental model for Dr. Tessier's work.

Originality: Excellent.

Despite the obvious importance of the concepts elaborated by Dr. Tessier not only for gout but for many inflammatory conditions there seem to be few others pursuing this line. Dr. Tessier has clearly identified an important problem and developed an innovative research programme around it.